

REMARKS

The disclosure stands objected to because blanks are present in the specification on pages 4, 5, and 28 for ATCC and hybridoma designations of the CTLA4 antibodies. Applicants respectfully request that the objection be held in abeyance until such time as there is allowable subject matter.

Status of the Claims

Claims 2-11 and 13-23 are pending. Claims 16-23 have been withdrawn from further consideration by the Examiner as being drawn to a non-elected invention. Claims 2-11, and 13-15 are currently under consideration. New claim 24 has been added to more particularly point out the invention. Support for claim 24 is found in the specification on page 14, lines 19-32.

Claim Objections

Claims 2-11 and 13 stand objected to under 37 C.F.R. §1.75(c) as allegedly being of improper form for failing to further limit the subject matter of a previous claim. Claim 1 has been canceled and claim 2 has been amended, thus obviating the objection.

Indefiniteness Rejection Under 35 U.S.C. § 112

Claim 7 stands rejected under 35 U.S.C. § 112 second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claim 7 has been amended according to the Examiner's suggestion to recite a human CTLA4 without the substitution at position 83,

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to correct an inadvertent typographical error in the claim and without altering the scope of the intended claim coverage. Applicants submit that this rejection is thus obviated.

Written Description Rejection Under 35 U.S.C. § 112

Claim 7 stands rejected under 35 U.S.C. § 112 first paragraph as allegedly failing to comply with the written description requirement. The Office alleges that claim 7 is drawn to a genus of antibodies having the same binding properties as a single species of CTLA4 antibody. The Office admits the disclosure sets forth the genus of antibodies to CTLA4, but alleges the specification provides only one species with the instantly recited properties. The Office thus concludes that claim 7 lacks written description support. The conclusion, however is erroneous.

The Written Description Standard

The written description requirement is met if the specification as originally filed reasonably conveys, to a person having ordinary skill in the art, that the Applicant had possession of the subject matter later claimed. *In re Kaslow*, 196 U.S.P.Q. 1089, (Fed. Cir. 1983). The specification need not describe the claimed invention in *ipsis verbis* to satisfy the written description requirement. *In re Edwards*, 196 U.S.P.Q. 465, (C.C.P.A. 1978). Moreover, the Office bears the burden of presenting evidence why a person skilled in the art would not recognize a description of the invention defined by the claims in the Applicant's specification. *Ex parte Sorenson*, 3 U.S.P.Q. 2d 1462, 1463 (B.P.A.I. 1987).

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The Office Has Not Met Its Burden

The Office has not presented any evidence to suggest why a skilled artisan reading the specification would not understand that the Applicant had possession of the claimed subject matter. Instead, the Office merely presents its conclusion as a bare assertion. The Board in *Sorenson, supra* at page 1463, specifically found such conduct to be a reversible error. Accordingly, Applicants respectfully request that the Office point out specific evidence to support its position or withdraw the rejection.

The Invention Is Supported By The Specification

Moreover, Applicants previously pointed to page 78, line 19-page 79, line 13; page 5, lines 22-25; and Figure 2B to support the amendment of claim 7. Figure 2 depicts binding of 3 different CTLA4 antibodies: antibody 25; antibody 26; and antibody 29. The specification discloses that these three antibodies are representative of all 9 CTLA4 specific antibodies produced (page 78, line 32-page 79, line 1). Figure 2b demonstrates antibody 26 binding to certain mutant CTLA4s is substantially reduced including the mutation at position 83 of SEQ ID NO:2 (referred to as E46, see page 79). More importantly, the specification also discloses that the mutation at position 83 drastically affects binding of 6 of the 9 antibodies produced (page 79, lines 1-5). The allegation that Applicants have provided only one species with the recited properties is therefore without merit. Applicants submit the specification provides written support for the claimed subject matter and accordingly, respectfully requests the rejection be withdrawn.

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The Rejections Under 35 U.S.C. § 103(a)

Claims 2-7, 10-11 and 13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,821,332 (Godfrey) and U.S. Patent No. 6,207,156 (Kuchroo). The Office alleges Kuchroo teaches monoclonal antibodies to CTLA4, but admits that Kuchroo does not teach antibody toxic-moiety conjugates. The Office alleges Godfrey teaches antibody-toxic moiety conjugates specific to ACT4, a polypeptide allegedly expressed only on activated T cells. The Office concludes the claimed invention is obvious in light of Godfrey combined with Kuchroo. The conclusion is erroneous.

The Claimed Invention Is Not Prima Facie Obvious

MPEP § 2143 provides the standard required to establish a prima facie case of obviousness. "First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine what the reference teaches. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references combined) must teach or suggest all the claim limitations."

The motivation to make the claimed invention and the reasonable expectation of success must both be found in the prior art, not the Applicant's disclosure. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). The references must be considered as a whole and must suggest the desirability, and thus the obviousness of making the combination. *Hodosh v. Block Drug Co., Inc.*, 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986); MPEP § 2141. The Patent and Trademark Office (PTO) bears the burden of

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initially establishing a prima facie case of obviousness. MPEP § 2142. The PTO has not met its burden in the instant case.

No Reasonable Expectation of Success Exists In Combining the Cited References

There would be no reasonable expectation of success in combining Kuchroo with Godfrey, because Godfrey discloses a CTLA4 specific antibody that is immunostimulatory. But nothing in any reference cited by the Office suggests conjugating a toxin to an immunostimulatory antibody would be successful. As admitted by the Office, the conjugated antibody to ACT4 disclosed by Godfrey was not immunostimulatory. As further admitted by the Office, the CTLA4 antibody disclosed by Kuchroo was. The Office admits that conjugation of a toxin to an antibody is supposed to target that cell for elimination. But nothing of record indicates that conjugating a toxin to a CTLA4 specific antibody would be successful, given that Kuchroo discloses that CTLA4 specific antibodies cause T cells to proliferate (i.e., are immunostimulatory). The Office suggests combining two compositions which have opposing outcomes (i.e., a toxin which eliminates cells combined with an antibody that causes the same cells to proliferate). At best, the combination might be merely obvious to try, but there was certainly no reasonable expectation of success that the combination would be successful. Obvious to try, however, is not the standard under 35 U.S.C. § 103. *In re O'Farrell*, 7 U.S.P.Q. 1673, 1680 (Fed. Cir. 1988). The Office is also reminded that the reasonable expectation of success must be found in the cited references. *In re Vaeck*, 20 U.S.P.Q. 2d 1438, 1442 (Fed. Cir. 1991). Applicants submit the Office has not met its burden in this regard and respectfully request the rejection be withdrawn.

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Applicants previously argued that no reasonable expectation of success existed in making the claimed combination because CTLA4 and ACT4 belonged to distinct families and each was a member of a distinct signaling pathway. In response, the Office argued the instant claims are drawn to a product and the motivation of the ordinary artisan to produce the instantly claimed product would not have been inhibited by the fact that CTLA4 and ACT4 belong to different families or the uniqueness of ACT4. The Office further argued antibody linked toxins to a variety of receptor families were well known at the time of the invention and the identification of cell surface molecules expressed predominantly on activated T cells provided the artisan with the opportunity to selectively eliminate activated T cells. There is nothing of record to support any of these statements. The Office is respectfully reminded that the burden of establishing a *prima facie* case of obviousness rests with the Office. MPEP § 2142. Applicants request that the Office cite a reference to support its position. Alternatively, if the Office is relying on the personal knowledge of the Examiner to support its position, Applicants request the submission of an affidavit pursuant 37 C.F.R. §1.104(d). Without such support Applicants submit the rejection must be withdrawn.

No Motivation To Combine The Cited References Exists

A skilled artisan would not be motivated to combine the cited references because Godfrey and Kuchroo teach contradictory outcomes. Targeting a cell with a toxic moiety attached to an ACT4 specific antibody is intended to eliminate the target cell. Targeting a cell with the CTLA4 antibody disclosed in Kuchroo is intended to make the target cell proliferate. The Office has not pointed to anything in either reference to establish why such a combination would be desirable. The references do not provide any motivation

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for a skilled artisan to combine them and the Office has not pointed to any knowledge generally available to a skilled artisan to suggest such a combination would be desirable. Accordingly, Applicants respectfully request withdrawal of the rejection.

Hamann Combined With Godfrey And Kuchroo Does Not Render Claims 8 And 9 Prima Facie Obvious

Additionally, claims 8-9 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Godfrey, combined with Kuchroo in view of U.S. Patent No. 5,773,001 (Hamann). Claim 8 recites the toxic moiety is a carbohydrate. Claim 9 recites the carbohydrate is calicheamicin. Hamann teaches antibodies conjugated with calicheamicin. Hamman does not teach targeting molecules expressed on activated T cells. Thus, Hamman does not teach targeting CTLA4. The Office relies on Hamann as allegedly teaching antibodies conjugated to carbohydrates generally, and calicheamicin specifically. Hamann, however, does not compensate for the deficiencies in the Godfrey and Kuchroo. A skilled artisan reading Hamann, would still have no reasonable expectation of success in combining Godfrey with Kuchroo, as Hamann only provides information on conjugating antibodies with calicheamicin--it does not address targeting CTLA4 or explain why an immunostimulatory antibody could be successfully conjugated to a toxin intended to kill the target cell of the antibody. Thus, claims 8 and 9 are not prima facie obvious. Applicants respectfully request withdrawal of the rejection.

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CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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